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Ambient Air Pollution Exposures and Risk of Parkinson Disease

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ABSTRACT

Background: Few epidemiologic studies have evaluated the effects of air pollution on risk of Parkinson's disease (PD).

Objective: We investigated the associations of long-term residential concentrations of ambient particulate matter (PM) less than 10μm in diameter (PM_{10}), less than 2.5μm in diameter ($PM_{2.5}$), and nitrogen dioxide (NO_2) in relation to PD risk.

Methods: Our nested case-control analysis included 1,556 self-reported physician-diagnosed PD cases identified between 1995-2006 and 3,313 controls frequency matched on age, sex, and race. We geocoded home addresses reported in 1995-1996 and estimated the average ambient concentrations of PM_{10}, $PM_{2.5}$ and NO_2 using a national fine-scale geo-statistical model incorporating roadway information and other geographic covariates. Air pollutant exposures were analyzed both as quintiles and continuous variables, adjusting for matching variables and potential confounders.

Results: We observed no statistically significant overall association between PM or NO_2 exposures and PD risk. However, in pre-planned subgroup analyses, a higher risk of PD was associated with higher exposure to PM_{10} ($OR_{Q5vs.Q1}$=1.65; 95% CI: 1.11, 2.45; p-trend=0.02) among women, and to $PM_{2.5}$ ($OR_{Q5vs.Q1}$=1.29; 95% CI: 0.94, 1.76; p-trend=0.04) among never smokers. In post-hoc analyses among female never smokers, both $PM_{2.5}$ (OR for Q_5vs.Q_1=1.79; 95% CI: 1.01, 3.17; p-trend=0.05) and PM_{10} (OR for Q_5vs.Q_1=2.34; 95% CI: 1.29, 4.26; p-trend=0.01) showed positive associations with PD risk. Analyses based on continuous exposure variables generally showed similar but non-significant associations.

Conclusions: Overall we found limited evidence for an association between exposures to ambient PM_{10}, $PM_{2.5}$, or NO_2 and PD risk. The suggestive evidence that exposures to $PM_{2.5}$ and PM_{10} may increase PD risk among female never smokers warrants further investigations.

Introduction

Air pollution is a complex and dynamic mixture consisting of particulate matter (PM), gases, organic components, and metals (Block et al. 2012). Numerous studies have consistently shown deleterious effects of air pollution on human health. Ambient PM, including PM_{10} (particles <10 μm in aerodynamic diameter) and $PM_{2.5}$ (particles <2.5 μm) and nitrogen oxides (NO_x) have been consistently associated with increased risk of pulmonary and cardiovascular diseases (Brook et al. 2004). Although results vary across studies, several epidemiologic studies report stronger associations among women than among men, particularly for older adults (Annesi-Maesano et al. 2003; Clougherty 2010).

Recent evidence suggests that air pollution may also adversely impact the integrity of the central nervous system (CNS) and may contribute to neurodegeneration through mechanisms such as chronic brain inflammation, oxidative stress, microglia activation, and white matter abnormalities (Block et al. 2012). For example, postmortem examination of brain tissues from residents in highly polluted urban areas showed elevated Aβ42 (Calderon-Garciduenas et al. 2008; Calderon-Garciduenas et al. 2012), hyper-phosphorylated tau (Calderon-Garciduenas et al. 2012), and α-synuclein accumulations (Calderon-Garciduenas et al. 2008); which have been implicated in the pathogenesis of major neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (PD). Animal studies further demonstrated that exposure to concentrated ambient PM led to increased levels of α-synuclein in midbrain (Levesque et al. 2011), loss of dopaminergic neurons in the substantia nigra (Veronesi et al. 2005), and elevation of pro-inflammatory factors in the brain (Levesque et al. 2011). Disruptions of the nasal and olfactory

epithelial barriers were also reported in dogs exposed to urban air pollutants high in PM (Calderon-Garciduenas et al. 2002; Calderon-Garciduenas et al. 2003). These changes closely resemble neuropathological alterations in brains of PD patients.

Few epidemiologic data have examined potential roles of ambient air pollutants in PD and findings are inconsistent (Finkelstein and Jerrett 2007; Kirrane et al. 2015; Palacios et al. 2014a; Palacios et al. 2014b; Ritz et al. 2015; Willis et al. 2010). We therefore investigated the association between ambient PM_{10}, $PM_{2.5}$, and nitrogen dioxide (NO_2) exposures and risk of PD in the Parkinson's, Genes and Environment (PAGE) study.

Methods

Study population

The PAGE study is a nested case-control study within the large prospective NIH-AARP Diet and Health Study. Detailed description of the NIH-AARP study has been described previously (Schatzkin et al. 2001). Briefly, the cohort was established in 1995-1996 by the National Cancer Institute to investigate the roles of diet and lifestyle in the development of cancers and other chronic diseases. Participants were 566,398 AARP (formerly known as the American Association of Retired Persons) members aged 50-71 years who resided in one of six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two US metropolitan areas (Atlanta, Georgia and Detroit, Michigan). At enrollment, participants completed a comprehensive baseline questionnaire on diet, demographic characteristics, health-related behaviors, and medical history.

PD case identification and control selection

PD patients in PAGE were identified from the follow-up survey conducted during 2004-2006 among surviving participants in the original cohort. On the survey, participants reported whether they had ever received a physician diagnosis of PD and the year of their first diagnosis in the following categories: before 1985, 1985-1994, 1995-1999, or in or after 2000. A total of 2,432 participants reported a PD diagnosis. Controls (n=3,548) were randomly selected from cohort participants who did not report a PD diagnosis on the follow-up questionnaire, and were frequency matched to cases by year of birth (in 5-year groups), sex, and race. Because residential information was collected at the baseline survey in 1995-1996, we excluded from our analyses 394 cases who reported a PD diagnosis before 1995. We also excluded 358 self-reported PD cases whose diagnosis was later denied by patients themselves or by their treating physicians in the diagnostic confirmation effort described below. Additionally, we excluded 124 self-reported cases with residential addresses that could not be geocoded (e.g., no valid ZIP code; PO Boxes only; outside U.S.). Of the controls, we excluded 221 with invalid addresses and 14 self-reported controls who were later confirmed by physicians to be cases. After these exclusions, we had a total of 1,556 PD cases with self-reported PD diagnosis in or after 1995 and 3,313 age-, sex-, and race-matched controls in the primary analyses. The PD case group included 700 physician-confirmed cases as described below and 856 self-reported cases that we were unable to reach for diagnostic confirmation. Compared to physician confirmed cases, cases without diagnostic confirmation were older at enrollment (64.3±4.8 vs 63.2±4.9 years) and were more likely to be ever smokers (58.3% vs. 52.5%), but they were less likely to be non-Hispanic whites (93.6% vs. 96.0%), to have college education or higher (44.6% vs. 56.1%), and to be physically active (≥5

times/week: 17.8% vs. 21.7%). They were however not statistically different from confirmed cases in gender, caffeine intake, and residential regions in the US and urban or rural setting.

Between 2007 and 2010, we contacted surviving PD patients to confirm the self-reported PD diagnosis. Detailed procedures were published previously (Chen et al. 2010). Briefly, we asked the self-reported cases to confirm their reports and to permit us to contact their treating physicians. We then asked the treating physicians, mostly neurologists, to complete a diagnostic questionnaire and to send us a copy of the patient's medical records pertaining to PD diagnosis. The medical records were subsequently reviewed by a movement disorder specialist from the research team (XH). A case was confirmed if: 1) the treating neurologist confirmed the diagnosis; or 2) if the medical record included a final PD diagnosis or evidence of two or more cardinal signs of PD (with one being resting tremor or bradykinesia), a progressive course, responsiveness to dopaminergic treatments, and absence of features that suggested an alternative diagnosis. Of the 1,069 responses from physicians received to date, 940 (87.9%) PD diagnoses were confirmed.

Exposure Assessment

We geocoded the primary addresses of study participants provided at the baseline survey (1995-1996) using ArcMap version 10 (ESRI, Redlands, CA), and used residential locations to estimate outdoor pollutant concentrations. Invalid addresses, such as those with no valid zip code, PO Boxes, and addresses outside the continental U.S. were flagged and removed from the analysis. Daily PM_{10}, $PM_{2.5}$ and hourly NO_2 concentration data were obtained from the U.S. Environmental Protection Agency (EPA) ambient air pollution-monitoring stations in the

contiguous U.S., described in detail elsewhere (Novotny et al. 2011; Sampson et al. 2013). Average ambient PM_{10} and $PM_{2.5}$ concentrations for year 1990 and 2000, respectively, were estimated at the residential locations using a regionalized national universal kriging model (Sampson et al. 2013). Ambient NO_2 concentrations for year 2006 were estimated using a land-use regressions model that combined fixed-site ambient monitoring station, satellite-derived ground-level and land-use measurements data (Novotny et al. 2011). The cross-validated R^2 value for the $PM_{2.5}$ model in year 2000 was 0.88, as previously reported (Sampson et al. 2013). In addition to residential information, the baseline survey also collected information on demographics and lifestyle factors including age, gender, race, smoking habit, caffeine intake, and physical activity.

Statistical Analysis

We estimated multivariate odds ratios (OR) and 95% confidence intervals (CI) from unconditional logistic regression separately for $PM_{2.5}$, PM_{10}, and NO_2 concentrations. Because little is known about the association of these air pollutants and PD, we defined exposures both in quintiles as well as continuous variables. Covariates included baseline age (in 5-year groups), gender, race (whites vs. nonwhites), smoking status (never smoker vs. ever smoker), caffeine intake (quintiles), region of the United States (northeast, midwest, west, south), and physical activity (never or rarely, times/week: <1, 1-2, 3-4, and ≥5). Because epidemiological studies have consistently observed lower risk of PD among smokers (Chen et al. 2010) and have suggested gender differences in both PD incidence (Haaxma et al. 2007) and risk factors (Weisskopf et al. 2007; O'Reilly et al. 2010; Chen et al. 2002), we performed additional analyses stratified by gender and baseline smoking status, and tested for potential interactions by

including a multiplicative interaction term in the regression model. We examined the statistical significance for a linear trend by including a continuous variable defined by the median value of each pollutant exposure quintile in the regression model. As these analyses indicated associations among women and never smokers, we further conducted post-hoc analyses and examined the association between each pollutant exposure and PD risk exclusively among female non-smokers. Among female non-smokers, we further conducted analysis stratified by moving status, defined by whether the participant maintained the same latitude and longitude coordinates between baseline and follow-up surveys. The primary analyses were conducted with all eligible cases, but we also conducted sensitivity analyses by limiting to physician confirmed cases. Finally, we performed additional sensitivity analyses stratified by Census regions of the US. We re-categorized the pollutant exposures into tertiles to preserve sample sizes in exposure categories. We did not do this analysis for the Midwest region due to very small sample size. All statistical analyses were conducted using SAS, version 9.1 (SAS Institute, Cary, NC). Significance tests were 2-tailed, with $\alpha = 0.05$.

Standard protocol approvals, registrations, and patient consents

Participants consented to the study by returning survey questionnaires. The study protocol was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences and the Special Studies Institutional Review Board of the National Cancer Institute.

Results

Baseline characteristics of the study population according to PD diagnosis are presented in Table 1. Compared with those without PD, PD cases were more likely to be men and have a college

education or above. They were also more likely to be never smokers and had lower caffeine intake. The majority of the PAGE participants lived in urban counties, and the percentage of urban versus rural dwellers were comparable between PD cases and selected controls. $PM_{2.5}$ was moderately correlated with PM_{10} and NO_2 (r=0.57 and 0.62, respectively), and NO_2 was also moderately correlated with both $PM_{2.5}$ and PM_{10} (r=0.58 for both).

Overall, we found no statistically significant associations between exposures to ambient PM_{10}, $PM_{2.5}$, or NO_2 and PD risk (Table 2). In a priori analyses stratified by gender (Table 3), high exposure to PM_{10} was associated with a higher risk of PD among women ($OR_{Q5vs.Q1}$= 1.65; 95% CI: 1.11, 2.45; p-trend = 0.02) but not among men (OR= 0.92; 95% CI: 0.73, 1.14; p-trend = 0.95). In a priori analyses stratified by smoking (Table 3), exposure to the highest quintile of $PM_{2.5}$ concentration was associated with a higher risk of PD among never-smokers ($OR_{Q5vs.Q1}$= 1.29; 95% CI: 0.94, 1.76; p-trend = 0.04). However, the P for interaction was not statistically significant in either analysis. Additional adjustment for US region modestly attenuated the associations without materially changing the results (data not shown). Further, in the stratified analyses by US regions, higher risk of PD was observed in the South for exposures to the highest tertile of $PM_{2.5}$ and PM_{10} among female and for the highest $PM_{2.5}$ tertile among never smokers (see Supplemental Material, Table S1). In post-hoc analyses among female never smokers (Table 4), higher PD risk was associated with increased exposures in the top two quintiles of $PM_{2.5}$ ($OR_{Q4vs.Q1}$= 2.38; 95% CI: 1.32, 4.31 and $OR_{Q5vs.Q1}$= 1.79; 95% CI: 1.01, 3.17; p-trend = 0.05) and in the top quintile of PM_{10} ($OR_{Q5vs.Q1}$= 2.34; 95% CI: 1.29, 4.26; p-trend 0.01). Additional adjustment for region did not materially change the results. Further sensitivity analysis stratified by US region showed significant higher risk of PD with high PM exposures among individuals

living in the South (see Supplemental Material, Table S2). For all analyses, weak positive associations were also found when $PM_{2.5}$ and PM_{10} exposures were defined as continuous variables, although most analyses did not reach statistical significance.

We conducted additional sensitivity analyses stratified by moving status among female non-smokers (see Supplemental Material, Table S3). Women who maintained the same residential latitude and longitude coordinates between baseline and follow-up surveys were classified as non-movers, while those with a change in either latitude or longitude were classified as movers. Among non-movers, the risk for PD increased monotonically with increasing exposures to PM_{10} concentrations ($OR_{Q5vs.Q1}$= 2.67; 95% CI: 1.20, 5.96; p-trend 0.01). However, no statistically significant trends were found among movers.

Similar results were observed in the sensitivity analyses restricted to physician confirmed cases. Higher exposure to PM_{10} was associated with a higher risk of PD among women ($OR_{Q5vs.Q1}$= 2.12; 95% CI: 1.19, 3.80; p-trend = 0.02), and higher exposure to $PM_{2.5}$ was associated with greater PD risk among never-smokers ($OR_{Q5vs.Q1}$= 1.26; 95% CI: 0.83, 1.92; p-trend = 0.19). In the analyses among female never smokers, higher PD risk was associated with the top two quintiles of $PM_{2.5}$ ($OR_{Q4vs.Q1}$= 2.69; 95% CI: 1.24, 5.85 and $OR_{Q5vs.Q1}$= 1.63; 95% CI: 0.76, 3.54; p-trend = 0.31) and the top quintile of PM_{10} ($OR_{Q5vs.Q1}$= 2.17; 95% CI: 0.97, 4.82; p-trend 0.12). No other statistically significant associations were observed.

Discussion

In this large nested case-control study of older adults, we did not find strong evidence for an association between exposures to ambient PM_{10}, $PM_{2.5}$, or NO_2 concentrations and risk for PD in older adults. However, subgroup analyses suggest that female nonsmokers exposed to higher concentrations of PM_{10} or $PM_{2.5}$ may have a higher risk for PD.

The deleterious effects of ambient air pollution on cardiovascular and pulmonary outcomes have been well documented (Block et al. 2012; Brook et al. 2004) and recent evidence provided key insights on how these adverse effects may also impact the brain (Block et al. 2012). As a complex mixture, air pollution likely exerts adverse effects on the brain through multiple interrelated mechanisms that may subsequently lead to neurodegenerative diseases such as PD (Block and Calderon-Garciduenas 2009). Systemic inflammation triggered by pollutant inflamed peripheral organs including the lung, gut, and cardiovascular system may contribute to the disruption of olfactory, respiratory, and blood-brain barriers (Block et al. 2012). These cascading events may work synergistically to enhance access of pollutants and systemic inflammatory mediators to the CNS, leading to neuroinflammation and neurotoxicity (Block and Calderon-Garciduenas 2009; Block et al. 2012; Calderon-Garciduenas et al. 2013). Chronic exposures to varying size and composition of PM have been shown to induce pathological hallmarks of PD, including neuroinflammation, aggregation of α-synuclein, and neuronal oxidative stress (Block et al. 2012; Calderon-Garciduenas et al. 2013), even in early childhood (Calderon-Garciduenas et al. 2013). Experimental data further demonstrates PD neuropathology in animals exposed to concentrated urban PM or diesel exhaust, including significant reduction of dopaminergic neurons in the substantia nigra (Veronesi et al. 2005), elevated α-synuclein in the midbrain

(Levesque et al. 2011), and activation of unfolded protein response in the striatum (Guerra et al. 2013). As a route of entry for air pollutants to the brain, evidence from animal studies suggests that the nasal cavity likely provides a direct transport pathway through which inhaled PM gain entry into the olfactory bulbs and successively into the brain and brainstem (Block et al. 2012; Calderon-Garciduenas et al. 2010; Calderon-Garciduenas et al. 2015). Interestingly, lesions of the olfactory bulb have been postulated as one of the earliest pathologic features of PD (Braak et al. 2003), with supporting epidemiologic evidence showing olfactory deficit as one of the most important prodromal symptoms of PD (Langston 2011). Alternatively, particles being cleared from the deep lung via the mucociliary escalator or those too large to enter the lung are swallowed and eventually end up in the gut. Thus, the sensory afferent of the dorsal vagus nerve located in the gastrointestinal tract has been postulated as another potential route of entry for air pollutants because of its ability to communicate directly with brain stem neurons (Block et al. 2012). The enteric plexuses along with the olfactory bulb have been proposed as key routes through which a neurotropic pathogen initiates the pathological process underlying sporadic PD (Hawkes et al. 2007). Indeed, Lewy body pathology has been found to start early in the enteric plexus of the stomach and the olfactory bulb (Hawkes et al. 2007). Therefore, investigations on air pollution and PD may not only improve our understanding of the pollutant effects on PD risk, but also elucidate underlying mechanisms involved in PD development and progression.

However, few epidemiologic studies have evaluated exposures to ambient air pollution in relation to PD risk, and the results have been mixed. Willis et al. (Willis et al. 2010) in their study of U.S. Medicare part A beneficiaries, found significantly increased incidence of PD among participants living in urban counties with high cumulative industrial release of manganese

(>75th percentile), as reported in the U.S. EPA Toxic Release Inventory database. A Canadian case-control study of two urban cities using PD cases from administrative dataset also reported a significant association of PD with exposures to ambient levels of manganese defined as manganese fraction in total suspended particulate (Finkelstein and Jerrett 2007). This study however did not find any associations between exposures to urban traffic and neighborhood levels of NO_2, markers of traffic-generated air pollution, and the risk for PD (Finkelstein and Jerrett 2007). The Nurses' Health Study recently reported a positive association between airborne mercury exposure and PD, particularly among never-smokers and among participants living in urban counties (Palacios et al. 2014a). Evaluation of PM exposures in the same prospective cohort however found no evidence to support an effect of air pollution on PD risk (Palacios et al. 2014b). A more recent study among farmers in Iowa and North Carolina reported borderline positive associations of PD with exposures to ozone and $PM_{2.5}$ in North Carolina, but not in Iowa (Kirrane et al. 2015). The recent publication by Ritz et al. (Ritz et al. 2015) reported an increased risk of PD with long-term exposure to NO_2 in a Danish population, specifically among those born or living in the capital city or provincial towns. Only two of these six existing epidemiologic studies investigated potential effect modification by sex and in both studies no significant sex-differences were observed (Finkelstein and Jerrett 2007; Ritz et al. 2015).

We planned a priori analyses stratified by gender and smoking status because gender differences exist in both PD prevalence and risk profiles (Haaxma et al. 2007) and smoking is an important risk factor for PD (Chen et al. 2010). Moreover, a number of epidemiologic studies on cardiovascular and respiratory health outcomes showed stronger adverse effects of air pollutants among women, particularly in studies of older adults and those using residential exposure

assessment (Clougherty 2010). Interestingly, in our analysis, a higher risk of PD was observed among women and never smokers exposed to greater levels of PM. While we cannot completely exclude the possibility that this finding is by chance, the observed modification is likely, at least in part, attributable to differences in exposure patterns and biological responses to air pollution between men and women (Clougherty 2010). Indeed, physiologic differences between the sexes, such as hormonal status or body size have shown to influence the biological transport of environmental toxicants (Clougherty 2010). Other biological traits such as lung size (Kim and Hu 1998, 2006), deposition of inhaled particles (Kim and Hu 2006), blood-gas barrier permeability (Brauner et al. 2009), and inflammation (Hoffmann et al. 2009) also differ by sex. Additionally, gender-related differences in occupation and lifestyle factors such as smoking and alcohol consumption, also likely play a role in differential exposure patterns between men and women (Clougherty 2010; Oiamo and Luginaah 2013). The evidence of sex-differences in susceptibility to air pollution remain unknown, and further investigation and reporting of sex-stratified results will be informative and may provide some insights into possible biological mechanisms.

The precise reasons for lack of a clear association of PD with $PM_{2.5}$ among women and with PM_{10} among never smokers are unknown but may reflect random or exposure assessment errors, or residual confounding rather than lack of neurotoxic effects. Interestingly, in analyses restricted to female never smokers, both $PM_{2.5}$ and PM_{10} were significantly associated with higher risk of PD. Indeed, both $PM_{2.5}$ and PM_{10} have been shown to exert neurotoxic effects on the brain. In addition to the well-documented effects on neuroinflammation and oxidative stress (Block and Calderon-Garciduenas 2009), $PM_{2.5}$ exposure may disrupt the blood-brain-barrier (Liu et al.

2015). Although much research has focused on small particles, recent data suggest that larger particles may also have neurotoxic effects. For instance, one *in vivo* study suggests that the peripheral inflammatory response to PM_{10} exposure in mice may trigger adverse effects in the brain (Farina et al. 2013). Another murine study reported evidence of neuroinflammation, oxidative stress and unfolded protein responses in striatum activated by inhaled exposure to coarse PM (Guerra et al. 2013).

The current study has a number of notable strengths. A key strength was the employment of finely resolved, validated, national air pollutant models based on residential address. Our study population was geographically diverse, which allowed for the assessment of a wider range of exposure gradients. Our relatively large sample size included over a thousand male and female PD cases. Further, we have conducted a number of sensitivity analyses, for example, by limiting analyses to physician confirmed cases and stratified analyses by region of residency. These results are consistent with the primary findings.

Our study also has several limitations. First, measurement of long-term air pollution exposure is prone to misclassification. In the current study, we used the outdoor concentration at the baseline residential address to characterize exposure. We do not have precise information on the concentrations in the micro-environments in which cases and controls spent their time. The specific years used for the prediction of different pollutants were based on the availability of the modeled air pollutant data. For this reason, the years of exposure assessment for $PM_{2.5}$ and NO_2 were after disease diagnosis. However, we did not expect that the particular prediction year being modeled would have made a substantial difference; for both $PM_{2.5}$ and NO_2 the correlations

between predictions in adjacent years are high (r>0.96). Nonetheless, because of declining PM and NO_2 levels since the 1990s, it may be possible that the "baseline" exposures to $PM_{2.5}$ and NO_2 were systematically underestimated. Second, the pollutant estimates we have are only representative of a portion of the participants' adulthood exposure, while earlier time frames may be at least as important. The time frame, severity, and type of air pollution exposures during an individuals' lifetime may be critical for evaluating deleterious effects of air pollution on PD pathology. Alarmingly, children residing in severely polluted Mexico City Metropolitan Area (MCMA) already exhibit symptoms seen in the premotor stage of PD, including olfactory disturbances and severe autonomic dysfunction (Calderon-Garciduenas et al. 2013). The presence of α-synuclein associated with PD pathology was also detected in the olfactory bulb, midbrain, and lower brainstem of MCMA children (Calderon-Garciduenas et al. 2013). Given the long duration of the preclinical stage of PD before overt motor symptoms appear, cumulative lifetime exposure assessments spanning from early child-adulthood would be ideal. Third, we only collected residential addresses and data on potential exposures to pollutants in the workplace were not available. Another limitation is that PD diagnosis was only asked once at the follow-up survey with categorical choices for the year of diagnosis, therefore some cases during the follow-up were inevitably missed and we were unable to perform more desirable risk-set sampling for controls. Further, PD case identification was based on self-reports. It is inevitable that some cases were missed and some were misdiagnosed. However, our validation study confirmed 88% of self-reported diagnoses among those with medical information available, and we excluded from the analysis cases with erroneous reports. Finally, although our cohort was relatively large, we still had only modest numbers of PD cases in some analyses; this, together

with potential measurement errors in exposure and outcome assessments, may have limited our ability to detect moderate associations.

In conclusion, although there was no statistically significant association between ambient air pollution and PD risk in this cohort of older adults overall, we found higher risk of PD among women and never smokers with exposures to high levels of $PM_{2.5}$ and $PM_{10.}$ These findings warrant further investigation.

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Table 1. Baseline characteristics of study participants in the NIH-AARP Diet and Health Study according to Parkinson's disease diagnosis after 1995[a]

	No PD	PD
N	3,313	1,556
Mean age in years (SD)	63.5 (4.8)	63.8 (4.9)
Men, %	73.5	74.2
Race, %		
Non-Hispanic White	94.4	94.7
Others	4.7	4.6
Missing	0.9	0.7
Education, %		
<12 years	20.7	20.5
High school	9.3	6.8
Some college	21.5	20.5
College and above	46.3	49.8
Missing	2.2	2.3
Physical activity, %		
Never or rarely	15.3	15.3
1-3 times / month	12.2	12.5
1-2 times / week	21.3	19.3
3-4 times / week	28.9	32.5
≥ 5 times / week	21.3	19.5
Missing	0.9	0.9
Caffeine intake (mg/day), Median (IQR)	235.8 (528.7)	194.0 (522.8)
Smokers, %		
Never	35.2	43.2
Past	55.7	50.6
Current	8.0	5.1
Missing	1.1	1.1
Region of US		
Northeast region	27.7	28.3
Midwest region	5.3	5.3
West region	31.5	33.1
South region	35.5	33.2
Residential setting		
Urban	92.0	92.9
Rural	8.0	7.1

Abbreviations: IQR = interquartile range (25%-75%); PD = Parkinson disease.

[a] Percentage may not sum to 100 due to missing values.

Table 2. Exposure to PM_{10}, $PM_{2.5}$, and NO_2 and risk of PD, NIH-AARP Diet and Health Study, 1995-2006

Exposure	PD / No PD	OR[a]	95% CI	OR[b]	95% CI
Quintiles of $PM_{2.5}$ ($\mu g/m^3$)					
4.4- <10.8	300/673	1.00	Referent	1.00	Referent
10.8- <12.3	319/652	1.11	0.91, 1.34	1.09	0.90, 1.33
12.3- <13.8	305/672	1.03	0.85, 1.25	1.02	0.84, 1.23
13.8- <15.4	307/667	1.04	0.86, 1.27	1.03	0.85, 1.25
15.4- 26.9	325/649	1.14	0.94, 1.38	1.11	0.92, 1.35
P_{trend}[c]		0.31			0.43
Continuous $PM_{2.5}$ ($\mu g/m^3$)[d]	1556/3313	1.02	0.95, 1.10	1.02	0.94, 1.10
Quintiles of PM_{10} ($\mu g/m^3$)					
14.3- <22.9	315/658	1.00	Referent	1.00	Referent
22.9- <25.1	295/679	0.91	0.75, 1.11	0.91	0.75, 1.10
25.1- <27.9	305/669	0.96	0.79, 1.16	0.96	0.79, 1.16
27.9- <33.8	317/657	1.02	0.84, 1.23	1.01	0.83, 1.22
33.8- 65.4	324/650	1.06	0.87, 1.28	1.05	0.86, 1.27
P_{trend}[c]		0.25			0.29
Continuous PM_{10} ($\mu g/m^3$)[d]	1556/3313	1.03	0.97, 1.09	1.02	0.97, 1.09
Quintiles of NO_2 (ppb)					
1.0- <7.7	312/659	1.00	Referent	1.00	Referent
7.7- <10.4	303/673	0.95	0.79, 1.15	0.96	0.80, 1.17
10.4- <13.1	311/662	0.99	0.82, 1.20	0.99	0.82, 1.20
13.1- <16.6	319/656	1.03	0.86, 1.25	1.01	0.83, 1.22
16.6- 34.2	311/663	1.00	0.82, 1.21	0.99	0.81, 1.20
P_{trend}[c]		0.76			0.96
Continuous NO_2 (ppb)[d]	1556/3313	1.02	0.95, 1.11	1.01	0.93, 1.10

Abbreviations: CI, confidence interval; OR, odds ratio; PD, Parkinson disease.
[a] All adjusted for age at baseline, sex and race.
[b] Additionally adjusted for education, caffeine intake, smoking status, and physical activity.
[c] Based on liner model through the quintile medians.
[d] Change per interquartile range (IQR); Exposure (IRQ): $PM_{2.5}$ (3.8 $\mu g/m^3$), PM_{10} (8.4 $\mu g/m^3$), NO_2 (7.3 ppb),.

Table 3. Exposure to PM_{10}, $PM_{2.5}$, and NO_2 and risk of PD, by gender and smoking status, NIH-AARP Diet and Health Study, 1995-2006

	PD / No PD	OR[a]	95% CI	PD / No PD	OR[a]	95% CI	P-int[d]
By sex:	Male			Female			
Quintiles of $PM_{2.5}$ ($\mu g/m^3$)							
4.4- <10.8	235/500	1.00	Referent	65/173	1.00	Referent	
10.8- <12.3	231/498	0.98	0.78, 1.22	88/154	1.46	0.99, 2.18	
12.3- <13.8	238/485	1.04	0.83, 1.30	67/187	0.93	0.62, 1.40	
13.8- <15.4	218/499	0.92	0.74, 1.16	89/168	1.38	0.93, 2.05	
15.4- 26.9	232/453	1.08	0.87, 1.36	93/196	1.20	0.81, 1.77	0.69
P_{trend}[b]		0.61			0.53		
Continuous $PM_{2.5}$ ($\mu g/m^3$)[c]	1154/2435	1.01	0.92, 1.10	402/878	1.02	0.88, 1.18	0.72
Quintiles of PM_{10} ($\mu g/m^3$)							
14.3- <22.9	258/497	1.00	Referent	57/161	1.00	Referent	
22.9- <25.1	222/516	0.83	0.67, 1.04	73/163	1.27	0.84, 1.93	
25.1- <27.9	222/490	0.89	0.72, 1.12	83/179	1.30	0.86, 1.95	
27.9- <33.8	231/462	0.98	0.78, 1.22	86/195	1.25	0.83, 1.87	
33.8- 65.4	221/470	0.92	0.73, 1.14	103/180	1.65	1.11, 2.45	0.06
P_{trend}[b]		0.95			0.02		
Continuous PM_{10} ($\mu g/m^3$)[c]	1154/2435	1.00	0.94, 1.07	402/878	1.09	0.98, 1.23	0.22
Quintiles of NO_2 (ppb)							
1.0- <7.7	243/498	1.00	Referent	69/161	1.00	Referent	
7.7- <10.4	238/504	0.98	0.79, 1.22	65/169	0.89	0.59, 1.35	
10.4- <13.1	222/495	0.92	0.73, 1.14	89/167	1.29	0.88, 1.92	
13.1- <16.6	239/479	1.01	0.81, 1.26	80/177	1.04	0.70, 1.55	
16.6- 34.2	212/459	0.94	0.75, 1.18	99/204	1.13	0.77, 1.66	0.39
P_{trend}[b]		0.71			0.42		
Continuous NO_2 (ppb)[c]	1154/2435	1.00	0.91, 1.10	402/878	1.06	0.90, 1.24	0.61

By smoking status:	Never Smokers			Ever Smokers			
Quintiles of $PM_{2.5}$ ($\mu g/m^3$)							
4.4- <10.8	106/212	1.00	Referent	193/453	1.00	Referent	
10.8- <12.3	120/236	1.03	0.75, 1.43	194/411	1.12	0.88, 1.43	
12.3- <13.8	136/243	1.16	0.85, 1.60	166/421	0.94	0.73, 1.20	
13.8- <15.4	156/231	1.38	1.01, 1.89	149/427	0.83	0.64, 1.07	
15.4- 26.9	154/243	1.29	0.94, 1.76	165/398	0.99	0.77, 1.27	0.13
P_{trend}[b]		0.04			0.36		
Continuous $PM_{2.5}$ ($\mu g/m^3$)[c]	672/1165	1.09	0.97, 1.22	867/2110	0.95	0.86, 1.06	0.27
Quintiles of PM_{10} ($\mu g/m^3$)							
14.3- <22.9	113/213	1.00	Referent	198/437	1.00	Referent	
22.9- <25.1	129/257	0.97	0.71, 1.33	164/417	0.89	0.69, 1.14	
25.1- <27.9	145/211	1.32	0.96, 1.81	156/449	0.79	0.61, 1.01	
27.9- <33.8	142/241	1.14	0.83, 1.56	171/409	0.94	0.74, 1.21	
33.8- 65.4	143/243	1.13	0.83, 1.55	178/398	1.01	0.79, 1.30	0.97
P_{trend}[b]		0.51			0.41		
Continuous PM_{10} ($\mu g/m^3$)[c]	672/1165	1.03	0.94, 1.13	867/2110	1.02	0.94, 1.10	0.91
Quintiles of NO_2 (ppb)							
1.0- <7.7	121/226	1.00	Referent	188/422	1.00	Referent	
7.7- <10.4	127/207	1.17	0.85, 1.60	171/461	0.85	0.66, 1.09	
10.4- <13.1	138/228	1.14	0.84, 1.55	169/428	0.89	0.70, 1.15	
13.1- <16.6	140/268	1.01	0.74, 1.37	178/380	1.06	0.83, 1.36	
16.6- 34.2	146/236	1.18	0.87, 1.61	161/419	0.87	0.67, 1.12	0.69
P_{trend}[b]		0.56			0.71		
Continuous NO_2 (ppb)[c]	672/1165	1.02	0.90, 1.15	867/2110	1.01	0.91, 1.13	0.86

Abbreviations: CI, confidence interval; OR, odds ratio; PD, Parkinson disease

[a] Adjusted for age at baseline, sex (except in sex stratified analyses), race, education, caffeine intake, smoking status (except in smoking stratified analyses), and physical activity.

[b] Based on liner model through the quintile medians.

[c] Change per interquartile range.

[d] P-interaction between pollutant exposures and sex (top portion) and smoking (bottom portion).

Table 4. Exposure to PM_{10}, $PM_{2.5}$, and NO_2 and risk of PD among female non-smokers (N=617), NIH-AARP Diet and Health Study, 1995-2006

Exposure	PD / No PD	OR[a]	95% CI	OR[b]	95% CI	P-int[e]
Quintiles of $PM_{2.5}$ ($\mu g/m^3$)						
4.4- <10.8	27/69	1.00	Referent	1.00	Referent	
10.8- <12.3	44/72	1.76	0.96, 3.23	2.01	1.09, 3.72	
12.3- <13.8	37/84	1.34	0.72, 2.49	1.65	0.86, 3.19	
13.8- <15.4	58/73	2.38	1.32, 4.31	3.19	1.68, 6.08	
15.4- 26.9	59/94	1.79	1.01, 3.17	1.90	1.05, 3.44	0.16
P_{trend}[c]			0.05		0.05	
Continuous $PM_{2.5}$ ($\mu g/m^3$)[d]	225/392	1.14	0.95, 1.38	1.12	0.93, 1.36	0.09
Quintiles of PM_{10} ($\mu g/m^3$)						
14.3- <22.9	24/63	1.00	Referent	1.00	Referent	
22.9- <25.1	39/81	1.43	0.77, 2.68	1.44	0.77, 2.70	
25.1- <27.9	50/78	1.81	0.99, 3.32	1.78	0.97, 3.29	
27.9- <33.8	51/90	1.65	0.90, 3.00	1.51	0.80, 2.88	
33.8- 65.4	61/80	2.34	1.29, 4.26	1.99	0.93, 4.26	0.47
P_{trend}[c]			0.01		0.16	
Continuous PM_{10} ($\mu g/m^3$)[d]	225/392	1.18	1.01, 1.39	1.09	0.88, 1.36	0.13
Quintiles of NO_2 (ppb)						
1.0- <7.7	42/76	1.00	Referent	1.00	Referent	
7.7- <10.4	31/72	0.81	0.45, 1.46	0.83	0.46, 1.51	
10.4- <13.1	46/60	1.47	0.84, 2.57	1.49	0.83, 2.68	
13.1- <16.6	46/93	1.00	0.58, 1.70	0.91	0.49, 1.69	
16.6- 34.2	60/91	1.35	0.80, 2.28	1.18	0.63, 2.21	0.63
P_{trend}[c]			0.19		0.54	
Continuous NO_2 (ppb)[d]	225/392	1.11	0.89, 1.38	1.00	0.77, 1.31	0.71

Abbreviations: CI, confidence interval; OR, odds ratio; PD, Parkinson disease
[a] Adjusted for age at baseline, race, education, caffeine intake, and physical activity.
[b] Additionally adjust for region (northeast, midwest, west, and south).
[c] Based on liner model through the quintile medians.
[d] Change per interquartile range.
[e] P-interaction between pollutant exposures and region.